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(54) Title of invention

## Pharmaceutical compositions

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PHARMACEUTICAL COMPOSITIONS

This invention relates to improvements in the formulation of anti-inflammatory drugs.

5        Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin and ibuprofen, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric ulceration when administered 10 orally. This side effect may be further enhanced in combination with other factors such as stress. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

15       Ranitidine is the approved name for N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethenediamine which is described and claimed in British Patent Specification 1,565,966. It is a potent histamine H<sub>2</sub>-antagonist which may be used in the 20 treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. It has now been discovered that mucosal 25 lesions of the gastrointestinal tract caused by systemic non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering ranitidine.

30       The present invention provides a pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and ranitidine or a physiologically acceptable salt thereof.

Particularly useful pharmaceutical compositions according to the invention are those in a form suitable for oral or rectal administration.

35       The systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally

also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azaproprazone, diclofenac, fenbufen, feprazone, fenclofenac, flu-  
5 fenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac and tolmetin. They may be used in the pharmaceutical compositions of the invention in their usual dosage amounts, e.g. 50mg - 1 g of aspirin, 10 - 100mg of indomethacin and 100 - 500mg of ibuprofen per dosage unit  
10- taken one or more times daily in accordance with the normal dosage regime for the drug in question.

It is preferred that ranitidine should be employed in the composition in the form of a physiologically acceptable salt. Such salts include salts of inorganic or organic  
15 acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate and fumarate salts. The hydrochloride salt is particularly preferred. The amount of ranitidine, preferably in the form of a physiologically acceptable salt, employed in the pharmaceutical composition  
20 of the invention will be an amount sufficient to reduce the gastrointestinal distress caused by the anti-inflammatory drug and will preferably be in the range of 10 - 200mg per dosage unit.

The pharmaceutical compositions of the invention  
25 may be presented in a conventional manner with the aid of at least one pharmaceutical carrier or excipient. The composition may take the form of, for example, tablets, capsules, powders, granules, solutions, syrups, suspensions, or suppositories prepared by conventional means with  
30 acceptable excipients. The composition may thus contain as excipients, for example, binding agents, compression aids, fillers, lubricants, disintegrants and wetting agents. If desired, other active ingredients may also be present in such compositions. Tablets may be coated in  
35 conventional manner, for example, with a suitable film-forming material such as methyl cellulose, ethyl cellulose and/or hydroxypropylmethyl cellulose or with sugar.

Liquid preparations may also contain, for example, edible oils such as peanut oil. Suppositories may contain, for example, fat-soluble or water miscible bases.

5 The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the anti-inflammatory drug and the ranitidine or ranitidine salt may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by 10 direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine.

15 Alternatively, the pharmaceutical compositions of the invention may be presented in a suitable controlled release form so that the ranitidine or its salt is rapidly made available for absorption and the non-steroidal anti-inflammatory drug is released more slowly. The pharmaceutical compositions may thus be presented for oral or rectal administration in a conventional manner associated 20 with controlled release forms.

25 The pharmaceutical compositions of the invention may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis, and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastro-intestinal side-effects.

30 In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1 - TABLETS

		<u>mg/tablet</u>
	(a)	
55	Ranitidine hydrochloride	168.00*
	Ibuprofen	400.00
	Lactose	557.00

mg/tablet

10	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
5	Compression weight	1000.00

\*Equivalent to 150 mg ranitidine base

The ranitidine hydrochloride and ibuprofen are sieved through a 250 µm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 12.5mm punches.

(b)

mg/tablet

15	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Microcrystalline cellulose	79.00
	Magnesium stearate	3.00
	Compression weight	500.00
20	The ranitidine hydrochloride and indomethacin are blended with the microcrystalline cellulose and magnesium stearate and compressed using 9.5mm punches.	

Example 2 - CAPSULES

25	(a)	<u>capsule</u>
	Ranitidine hydrochloride	168.00
	Ibuprofen	400.00
	Starch 1500 **	228.00
	Magnesium stearate	4.00
30	Fill weight	800.00

\*\* A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The ranitidine hydrochloride and ibuprofen are sieved through a 250 µm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

	(b)	<u>mg/capsule</u>
	Ranitidine hydrochloride	168.00
	Indomethacin	50.00
	Starch 1500	80.50
5	Magnesium stearate	1.50
	Fill weight	300.00
10	The ranitidine hydrochloride and indomethacin are sieved through a 250 $\mu\text{m}$ sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.	

CLAIMS

1. A pharmaceutical composition comprising a systemic non-steroidal anti-inflammatory drug and ranitidine or a physiologically acceptable salt thereof.  
5
2. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is indomethacin.
3. A pharmaceutical composition as claimed in claim 2 which contains 10 - 100 mg of indomethacin and 10 - 200  
10 mg of ranitidine or a physiologically acceptable salt thereof per unit dose.
4. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is ibuprofen.
5. A pharmaceutical composition as claimed in claim 4 which contains 100 - 500 mg of ibuprofen and 10 - 200 mg  
15 of ranitidine or a physiologically acceptable salt thereof per unit dose.
6. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is aspirin.
- 20 7. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is fenoprofen.
8. A pharmaceutical composition as claimed in claim 1 in which the anti-inflammatory drug is ketoprofen.
9. A pharmaceutical composition as claimed in claim 1  
25 in which the anti-inflammatory drug is naproxen.
10. A pharmaceutical composition as claimed in claim 1

in which the anti-inflammatory drug is mefenamic acid.

11. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is diflunisal.

12. A pharmaceutical composition as claimed in claim 1  
5 in which the anti-inflammatory drug is benorylate.

13. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is azapropazone.

14. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is diclofenac.

10 15. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is fenbufen.

16. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is feprazone.

17. A pharmaceutical composition as claimed in claim 1  
15 in which the anti-inflammatory drug is fenclafenac.

18. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is flufenamic acid.

19. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is flurbiprofen.

20. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is oxyphenbutazone.

21. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is phenylbutazone.

22. A pharmaceutical composition as claimed in claim 1  
25 in which the anti-inflammatory drug is piroxicam.

23. A pharmaceutical composition as claimed in claim 1  
in which the anti-inflammatory drug is sulindac.

24. A pharmaceutical composition as claimed in claim 1

in which the anti-inflammatory drug is tolmetin.

25. A pharmaceutical composition as claimed in any of claims 1 to 24 also including at least one pharmaceutical carrier or excipient.

5 26. A pharmaceutical composition as claimed in any of claims 1 to 25 in a form suitable for oral or rectal administration.

27. A pharmaceutical composition as claimed in any of claims 1 to 26 in which the ranitidine is used in the

10 form of the hydrochloride salt.

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